JP 03-83925

Translated from Japanese by the Ralph McElroy Translation Company
910 West Avenue, Austin, Texas 78701 USA

Code: 5000-72813

JAPANESE PATENT OFFICE
PATENT JOURNAL
KOKAI PATENT APPLICATION NO. HEI 3[1991]-83925

Int.Cl.[5]: A61K 31/557
9/06
47/10
A 61K 47/12

Sequence Nos. for Office Use: 7252-4C
7624-4C
7624-4C

Filing No.: Hei 1[1989]-224047

Filing Date: August 29, 1989

Publication Date: April 9, 1991

No. of Claims: 5 (Total of 8 pages)

Examination Request: Not requested

EXTERNAL PREPARATIONS CONTAINING PROSTAGLANDIN E1

Inventors: Kanji Noda
320-93 Oaza Tsunematsu
Tsukushino City, Fukuoka-ken

Kanehito Kamikama
1716-80 Nagamine-cho
Kumamoto City, Kumamoto-ken

Tetsuyoshi Irie
14-25-8 Oe 2-chome
Kumamoto City, Kumamoto-ken

Hidetoshi Arima
21-7 Oe 1-chome
Kumamoto City, Kumamoto-ken

Hirotoshi Adachi
3275-6 Kengun-cho
Kumamoto City, Kumamoto-ken

Masaru Saida
855-75 Kokura, Motoyama-cho,
Miyaki-gun, Saga-ken

Tadanori Yano
1517-11 Aza Yanagii-cho
Tashiro Gai-cho
Torisu City, Saga-ken

Masahiko Noda
1542-7 Oaza Kasahara
Nakahara-cho, Miyaki-gun,
Saga-ken

Takafumi Manako
592-7 Oaza Harakoga
Nakahara-cho, Miyaki-gun,
Saga-ken

Michyuki Sakai
786-1 Daikan-cho, Tashiro
Torisu City, Saga-ken

Minoru Wada
2-907 Higashi-cho
Torisu City, Saga-ken

Applicant:

Hisamitsu Pharmaceutical Co., Ltd.
408 Daikan-cho, Tashiro
Torisu City, Saga-ken

Claims

1. External preparations containing prostaglandin E1, characterized by incorporating organic acids as stabilizers in compositions consisting of prostagladin E1, saturated fatty alcohols and glycols.

2. External preparations containing prostaglandin E1, characterized by incorporating organic acids as stabilizers in compositions consisting of prostaglandin E1, saturated fatty alcohols, glycols and absorption accelerators.

3. Ointment preparations containing prostaglandin E1, characterized by consisting of prostaglandin E1, saturated fatty alcohols, glycols and lactic acid and by adjusting the pH of the compositions to 3.0-5.0.

4. Ointment preparations containing prostaglandin E1, characterized by consisting of prostaglandin E1, saturated fatty alcohols, glycols, absorption accelerators and lactic acid and by adjusting the pH of the compositions to 3.0-5.0.

5. External preparations containing prostaglandin E1 of Claim 1, characterized by consisting of 0.0001-10 wt% prostaglandin E1, 15-45 wt% saturated fatty alcohols, 50-85 wt% glycols and 0.005-1.0 wt% organic acid and by adjusting the pH of the compositions to 3.0-5.0.

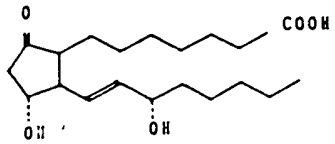
Detailed explanation of the invention

Industrial application field

This invention pertains to external preparations formed by containing prostaglandin E1 as the active component and having excellent stability and transdermal absorption property and drug efficacy.

Prior art

As shown in the structure below, prostaglandin E1 (hereafter, abbreviated as PGE1) is a compound of complex structure containing multifunctional groups in the molecule, including a double bond, hydroxyl groups or oxo groups. Moreover, PGE1 possesses various pharmacological activities even at microquantities, and it may be used as a thrombus treatment agent, antihypertensive agent, decubitus treatment agent, skin ulcer treatment agent, psoriasis treatment agent and hair growth drug.



However, as is obvious from the chemical structure shown above, PGE1 is in general a quite unstable compound, and is easily decomposed by acids, alkali, heat or light. Particularly, it undergoes a dehydration reaction in acidic conditions or under heating and converts to prostaglandin A1. Also, it is known to undergo isomerization under alkaline conditions and converts to prostaglandin B1.

Therefore, it is strongly desirable to improve the stability, especially over a long period of time, when PGE1 is utilized in drug preparation to produce pharmaceuticals. As such, there are many investigations attempting to stabilize the above said unstable compound PGE1. For

example, it has been known that there were compositions in which methylhesperidin was added as a stabilizer for prostaglandins (Japanese Kokai Patent Application No. Sho 53[1978]-127815), compositions in which citric acid esters were added (Japanese Kokai Patent Application No. Sho 53[1978]-127816), compositions in which phthalic acid esters were added (Japanese Kokai Patent Application No. Sho 53[1978]-127818), preparations using nonionic surfactants (for example, sorbitan monolaurate, sorbitan monopalmitate and sorbitan monostearate) (Japanese Kokai Patent Application No. Sho 53-148518), preparations incorporated with cellulose derivatives (Japanese Kokai Patent Application No. Sho 54[1979]-77497), medicinal materials containing silicone resins (Japanese Kokai Patent Application No. Sho 54[1979]-135495), compositions in which prostaglandins were incorporated into solvents containing specific propylene glycol diesters (Japanese Kokai Patent Application No. Sho 58[1983]-128325), and compositions which utilized etherified [sic; esterified] cyclodextrins for inclusion (Japanese Kokai Patent Application No. Sho 59[1984]-10525).

Problems to be solved by the invention

However, despite the fact that it is necessary to consider the stability of the drug preparations in particular when the unstable PGE1 showing useful pharmacological activity is used as a drug component in drug preparation, there has been insufficient investigation on the drug preparation for transdermal application, and there is no drug preparation with satisfactory stability, transdermal absorbing property and drug efficacy.

Means to solve the problems

Therefore, the present inventors had conducted vigorous investigations and many studies aiming at developing PGE1-containing external preparations that could solve the aforementioned various problems. That is, based on the conditions of incorporating PGE1 and having PGE1 stability over time, it was aimed at developing a formulation composition for an external vehicle having better stability and a drug formulation having good human transdermal absorption, and furthermore, the most optimum drug preparations that can be applied for treating subjects having target diseases. As a result, it was discovered that by incorporating organic acids, especially lactic acid, as stabilizers into certain ointment base vehicles, and by adjusting the pH of the preparations to the acidic region, the decomposition of PGE1 was significantly suppressed and all the aforementioned drawbacks were solved, achieving the present invention.

That is, the present invention provides target external preparations of PGE1 by incorporating PGE1 in base vehicles formed from saturated fatty alcohols, glycols and organic acids, and according to needs, absorption accelerators may be incorporated in the base vehicle.

To describe the present invention in more detail, the saturated fatty alcohols of the present invention are saturated fatty alcohols having 16-24 carbon atoms or their mixture and are preferably saturated monohydric primary alcohols. Among them, the particularly preferred ones are cetyl alcohol, stearyl alcohol and behenyl alcohol. Additionally, the saturated fatty alcohols are incorporated at 15-45 wt% based on the total weight, and preferably at 20-30 wt%.

The glycols are propylene glycol or butylene glycol (preferably 1,3-butylene glycol), and one or a mixture of two or more of these are utilized at 50-85 wt% based on the total weight, and preferably at 60-75 wt%. And, the organic acids are citric acid, succinic acid, tartaric acid, lactic acid, etc., and among them, lactic acid is the most preferred. Also, if the organic acids are incorporated in such a way that the pH of a 20% suspension of said composition is controlled in the acidic region, or more desirably within the range of 3.0-5.0, PGE1 can be further stabilized. The amount of incorporation is 0.005-1.0 wt%, and more preferably 0.01-0.5 wt%. Also, the active component PGE1 is incorporated at 0.0001-10 wt%, and preferably 0.001-1 wt%.

In addition to the aforementioned base vehicle and active components, it is desirable to incorporate absorption accelerators for the purpose of further promoting the absorption efficiency of the transdermal absorption. As the absorption accelerators, 1-dodecylazacycloheptan-2-one, 1-(2-(decylthio)ethyl)azacycloheptan-2-one, dimethyl sulfoxide, fatty alcohols such as lauryl alcohol or oleyl alcohol, crotamiton, fatty acids such as lauric acid or oleic acid, or terpenes such as l-menthol are utilized. The amount of application of the absorption accelerators is 0.01-8 wt% based on the total amount, and it is preferable that 0.1-5 wt% is incorporated.

Additionally, other additives may be incorporated according to needs including, for example, supplementary solvents (for example, polyethylene glycols having molecular weights of 100-800, glycerol, diethylene glycol monoethyl ether, propylene glycol monomethyl ether, dipropylene glycol monomethyl ether, 2,2-dimethyl-1,3-dioxolan-4-methanol, etc.) at under 25 wt%, plasticizers (for example, polyethylene glycols having molecular weights of 800-20,000, 1,2,6-hexanetriol, sorbitol, etc.) at under 15 wt%, coupling agents (for example, saturated fatty acids having carbon numbers of 16-24 such as stearic acid, palmitic acid, fatty acid amides such as oleamide, palmitamide, stearamide and behenamide, fatty acid esters having carbon number of 16-24 such as sorbitan monostearate, polyethylene glycol monstearate and propylene glycol monostearate, and other corresponding fatty acid esters of oleic acid and palmitic acid) at under 15 wt%. Also, the amount of incorporation of the aforementioned supplementary solvents and plasticizers is preferably at above 20 wt% for the drug preparation.

Moreover, it is preferable that, in addition to the aforementioned each vehicle, antioxidants (for examples, ethylenediaminetetraacetic acid, ether chelating agents, propyl gallate, butylated oxyanisole [sic; hydroxyanisole], etc.), surfactants, etc., are incorporated to further improve the stability of the drug preparation.

Next, in the production of the PGE1-containing ointment drug preparation of the present invention, saturated fatty alcohol (15-45 wt%), glycols (50-85 wt%), organic acids (0.005-1.0 wt%) and according to needs, absorption accelerator (0.01-8 wt%), or other additives are formulated and heated until dissolved at 80-95°C and mixed in the presence or absence of nitrogen gas.

Next, the mixture is cooled while mixing at room temperature. This is followed by incorporating active component PGE1(0.0001-10 wt%)-ethanol solution, mixing and agitating in the presence or absence of nitrogen gas, while controlling the pH in the acid region, and preferably in the pH range of 3.0-5.0 to produce the ointment drug preparation.

Application examples are carried out below to further describe the present invention more specifically.

Application Example 1

Stearyl alcohol 0.95 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 0.704 g and 1,3-butylene glycol 6.335 g as the glycol, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 is added and the composition is obtained by agitation and mixing.

Application Example 2

Stearyl alcohol 0.949 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 0.703 g and 1,3-butylene glycol 6.333 g as the glycols, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 5 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 3

Stearyl alcohol 0.949 g, cetyl alcohol 0.799 g and behenyl alcohol 0.899 g as the saturated fatty alcohols, propylene glycol 0.702 g and 1,3-butylene glycol 6.331 g as the glycols, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 10 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 4

Stearyl alcohol 0.95 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 7.039 g as the glycol, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 5

Stearyl alcohol 0.95 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 2.112 g and 1,3-butylene glycol 4.927 g as the glycols, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 is added and the composition is obtained by agitation and mixing.

Application Example 6

Stearyl alcohol 1.0 g, cetyl alcohol 0.5 g as the saturated fatty alcohols, propylene glycol 0.67 g and 1,3-butylene glycol 6.42 g as the glycols, PEG-6000 0.5 g and 1,2,6-hexanetriol 0.3 g as the plasticizers, sorbitan monostearate 0.2 g as the coupling agent, 1-dodecylazacycloheptan-2-one 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 100 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 7

Stearyl alcohol 2.5 g, cetyl alcohol 1.0 g and behenyl alcohol 1.0 g as the saturated fatty alcohols, propylene glycol 1.265 g and 1,3-butylene glycol 3.735 g as the glycols, 1,2,6-hexanetriol 0.10 g as the plasticizer, polyoxyethylene glycol monostearate 0.09 g as the coupling agent, 1-(2-(decylthio)ethyl)azacyclopentan-2-one 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 10 μg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 8

Stearyl alcohol 1.5 g as the saturated fatty alcohol, propylene glycol 3.4 g and 1,3-butylene glycol 5.095 g as the glycols, and lactic acid 0.005 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 100 μg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 9

Stearyl alcohol 2.0 g as the saturated fatty alcohol, 1,3-butylene glycol 6.595 g as the glycols, sorbitan monostearate 0.2 g as the coupling agent, PEG-6000 0.3 g as the plasticizer, oleic acid 0.8 g as the absorption accelerator and lactic acid 0.1 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 5 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 10

Stearyl alcohol 1.35 g, cetyl alcohol 1.0 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 0.609 g and 1,3-butylene glycol 5.29 g as the glycols, stearic acid 0.2 g as the coupling agent, PEG-6000 0.3 g as the plasticizer, l-menthol 0.3 g as the absorption accelerator and lactic acid 0.001 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 50 mg PGE1 are added and the composition is obtained by agitation and mixing.

Application Example 11

Stearyl alcohol 1.5 g, cetyl alcohol 1.0 g and behenyl alcohol 1.0 g as the saturated fatty alcohols, propylene glycol 2.264 g and 1,3-butylene glycol 3.735 g as the glycols, 1,2,6-hexanetriol 0.25 g as the plasticizer, polyethylene glycol monostearate 0.24 g as the coupling agent, and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 is added and the composition is obtained by agitation and mixing.

Application Example 12

Stearyl alcohol 0.5 g and cetyl alcohol 0.5 g as the saturated fatty alcohols, propylene glycol 0.67 g and 1,3-butylene glycol 6.42 g as the glycols, PEG-6000 0.6 g and

1,2,6-hexanetriol 0.4 g as the plasticizers, sorbitan monostearate 0.3 g as the coupling agent and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 100 mg PGE1 are added and the composition is obtained by agitation and mixing.

Comparative Example 1

Stearyl alcohol 0.95 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 0.704 g and 1,3-butylene glycol 6.345 g as the glycol, lauryl alcohol 0.3 g as the absorption accelerator are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 is added and the composition is obtained by agitation and mixing.

Comparative Example 2

White petrolatum 8.299 g, bleached beeswax 0.8 g, stearyl alcohol 0.3 g, cholesterol 0.3 g and lauryl alcohol 0.3 g as the absorption accelerator are added together and heated to dissolve on a water bath by agitation. This is followed by sealing, and cooling at room temperature by agitation. To this base vehicle, 1 mg PGE1 is added and the composition is obtained by agitation and mixing.

Comparative Example 3

Stearyl alcohol 0.95 g, cetyl alcohol 0.8 g and behenyl alcohol 0.9 g as the saturated fatty alcohols, propylene glycol 0.705 g and 1,3-butylene glycol 6.335 g as the glycol, lauryl alcohol 0.3 g as the absorption accelerator and lactic acid 0.01 g as the stabilizer are added together and heated to dissolve on an oil bath at 95°C by agitation. This is followed by sealing, and cooling at room temperature by agitation and mixing to obtain the composition.

Experimental Example 1 Stability test

In order to investigate the stability of PGE1 in the ointment drug preparations of the present invention, 2 g of each of the ointments of the Application Examples 1-10 and those of Comparative Examples 1-2 were filled in aluminum tubes coated with phenol resin on the inner side, and after storing for one month at 40°C in a constant-temperature oven, the residual amounts of prostaglandin were quantified by liquid chromatography. A column filled with octadecylsilylated silica was used for the liquid chromatography, and the moving phase was a mixed solution of 0.01M KH_2PO_4-acetonitrile, and the detection was conducted at 201 nm. The results are shown in Table 1.

Table 1

① 試料	② PGE1 残存率 (%)
③ 実施例1の軟膏製剤	92.7
実施例2の軟膏製剤	92.4
実施例3の軟膏製剤	92.6
実施例4の軟膏製剤	91.8
実施例5の軟膏製剤	91.4
実施例6の軟膏製剤	90.9
実施例7の軟膏製剤	90.7
実施例8の軟膏製剤	91.0
実施例9の軟膏製剤	87.2
実施例10の軟膏製剤	90.2
④ 比較例1の軟膏製剤	60.2
比較例2の軟膏製剤	28.9

Key: 1 Sample
2 Residual rate
3 Ointment drug preparation of Application Example
4 Ointment drug preparation of Comparative Example

By comparing the results of the ointment drug preparations of the present invention to those of the Comparative Examples 1 and 2, it was found that the decomposition of PGE1 was significantly suppressed by adding lactic acid as a stabilizer.

Experimental Example 2 Test of skin blood flow rate

In order to confirm the localized efficacy of the ointment drug preparation of the present invention, determination of skin blood flow rate was conducted.

The compositions obtained in Application Examples 1, 2, and 3, and in Comparative Example 3 were applied openly at 5 mg each on a 1 x 1 cm area of the back skin of hairless mice anesthetized with urethane. The blood flow rate was determined before application and at 0.5, 1,

2, and 3 h after application, using a laser Doppler blood flowmeter. The differences before and after application were determined as Δv and used as the results, which are shown in Figure 1.

From the test results, it was found that the ointment drug preparations of the present invention showed significant increases of skin blood flow, compared to the case of Comparative Example 3 where PGE1 was not incorporated; additionally, it was found that the activity was maintained until 3 h after application, showing that the ointment drug preparation of the present invention was sufficiently absorbed transdermally while having sufficient drug efficacy.

Experimental Example 3 Transdermal testing

In order to confirm the transdermal absorption of the ointment drug preparation of the present invention by local application, determination of transdermal test of PGE1 was conducted.

A suitable amount of ^{3}H-PGE1 was added to the ointment drug preparations obtained in Application Examples 1, 4, and 5, and in Comparative Example 2 and mixed with agitation. Each ointment drug preparation was applied at 10 mg on the extracted back skin of hairless mice attached with a Loveday model diffusion cell. Physiological saline solution was used as the receptor phase, and a transdermal test was conducted at 25°C. The results are shown in Figure 2.

From the test results, it was found that the ointment drug preparations of the present invention showed significant transdermal absorption property, compared to the case of hydrophilic petrolatum of Comparative Example 2, and that the difference in transdermal absorption property was significantly affected by the difference in the ointment composition.

Function and effect of the invention

As is clear from the result of the aforementioned stability test, the ointment drug preparation of the present invention is extremely desirable because the drug composition can significantly inhibit PGE1 decomposition. Furthermore, the drug preparations are extremely stable so that they can be stored for a long period of time, and therefore, it is desirable for quality control purposes and is the most suitable for product commercialization. Additionally, the test of skin blood flow rate showed a significant increase of the skin blood rate and it was also found that the effect could be maintained for a few hours. This sufficiently underscores the fact that the ointment drug preparation of the present invention is smoothly absorbed transdermally, which results in the expression of the drug efficacy. Thus it is desirable for formulating drug preparations.

Additionally, in the transdermal testing, it showed significant transdermal absorption property, and it was found that the transdermal absorption property was markedly affected by the difference in the ointment compositions and that the results showed how superior the drug composition of the ointment of the present invention is.

Accordingly, the ointment drug preparation of the present invention is extremely superior on the stability of PGE1, the expression of the pharmacological activity and the transdermal absorption property. As an ointment drug preparation for the purpose of local application, it can be expected to be utilized in the treatment of Raynaud's disease, decubitus, skin ulcers, psoriasis, arteriosclerosis, etc., as well as being applied as a drug for hair growth.

Particularly, solving the problem of stabilizing PGE 1, which is the necessary condition for ointment drug preparation, is a matter of utmost importance in the drug preparation and is extremely useful to the pharmaceutical industry.

Bried description of the figures

Figure 1 shows the experimental results of skin blood flow when the drug preparation of the present invention was locally applied. The vertical axis shows the difference of blood flow rate before and after application of the compositions as Δv while the horizontal axis shows the lapsed time of the time course after application of the compositions.

Figure 2 shows the experimental results of the test of transdermal absorption when the drug preparation of the present invention was locally applied. The vertical axis shows the ratio of the amount of transdermal absorption of PGE1 to the amount of application, while the horizontal axis shows the lapsed time of the time course after the compositions are applied.

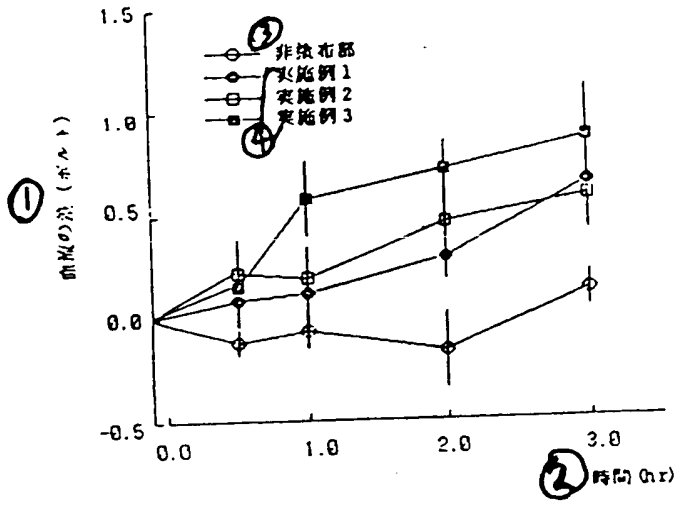


Figure 1

Key: 1 Difference in blood flow (volts)
2 Time
3 Nonapplied portion
4 Application Example

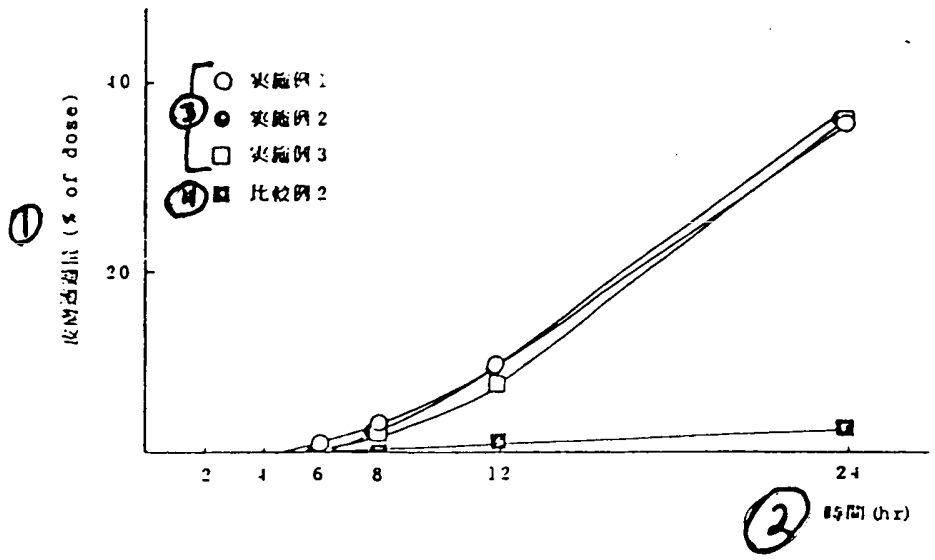


Figure 2

Key:
1 Amount of transdermal absorption
2 Time
3 Application Example
4 Comparative Example

Translated from Japanese by the Ralph McElroy Co., Custom Division
910 West Avenue, Austin, Texas 78701 USA

Code: 5000-72812

JAPANESE PATENT OFFICE
PATENT JOURNAL
KOKAI PATENT APPLICATION NO. HEI 3[1991]-83926

Int.Cl.[5]:	A61K 31/557 9/06 47/10
Sequence Nos. for Office Use:	7552-4C 7624-4C 7624-4C
Filing No.:	Hei 1[1989]-224048
Filing Date:	August 29, 1989
Publication Date:	April 9, 1991
No. of Claims:	2 (Total of 8 pages)
Examination Request:	Not requested

OINTMENT COMPOSITIONS

Inventors:

Kanji Noda
320-93 Oaza Tsunematsu
Tsukushino City, Fukuoka-ken

Kanehito Kamikama
1716-80 Nagamine-cho
Kumamoto City, Kumamoto-ken

Tetsuyoshi Irie
14-25-8 Oe 2-chome
Kumamoto City, Kumamoto-ken

Hidetoshi Arima
21-7 Oe 1-chome
Kumamoto City, Kumamoto-ken

Hirotoshi Adachi
3275-6 Kengun-cho
Kumamoto City, Kumamoto-ken

Masaru Saida
855-75 Kokura, Motoyama-cho,
Miyaki-gun, Saga-ken

Tadanori Yano
1517-11 Aza Yanagii-cho
Tashiro Gai-cho
Torisu City, Saga-ken

Masahiko Noda
1542-7 Oaza Kasahara
Nakahara-cho, Miyaki-gun,
Saga-ken

Takafumi Manako
592-7 Oaza Harakoga
Nakahara-cho, Miyaki-gun,
Saga-ken

Michyuki Sakai
786-1 Daikan-cho, Tashiro
Torisu City, Saga-ken

Minoru Wada
2-907 Higashi-cho
Torisu City, Saga-ken

Applicant: Hisamitsu Pharmaceutical Co., Ltd.
408 Daikan-cho, Tashiro
Torisu City, Saga-ken

Representative: Hirotaka Nakatomi

[There are no amendments to this patent.]

Claims

1. Ointment compositions characterized by containing prostaglandin E_1-inclusive esterified cyclodextrins as the active components.

2. Ointment compositions characterized by being formed from prostaglandin E_1-inclusive esterified cyclodextrins as the active components, from saturated fatty alcohols, glycols, and/or absorption accelerators.

Detailed explanation of the invention

Industrial application field

This invention pertains to ointment compositions that are formed by incorporating prostaglandin E_1-inclusive esterified cyclodextrins (hereafter, abbreviated as PGE_1-ECD) as the active component and have excellent stability and transdermal absorption as well as drug efficacy.

Prior art

Prostaglandin E_1 (hereafter, abbreviated as PGE_1) is known to have various specific pharmacological activities (for examples, blood platelet coagulation suppressing activity, peripheral vasodilation activity, etc.). Among them, peripheral vasodilation activity shows a particularly significant effect, and drug preparations having this activity are widely investigated. However, PGE_1 is, in general, a quite unstable compound and is easily decomposed by acids, alkali, heat or light. Particularly, it undergoes a dehydration reaction in acidic conditions or when heated and converts to prostaglandin A_1. Also, it is known to undergo isomerization under alkaline conditions and converts to prostaglandin B_1.

Therefore, it is strongly desirable to improve stability, especially over a long period of time, when PGE_1 is utilized in drug preparations to produce pharmaceuticals. As such, there are many investigations attempting to stabilize the above-mentioned unstable compound PGE_1. Among them, there was the Japanese Kokai Patent Application No. Sho 59 [1984]-10525, in which it is disclosed that the stability of PGE_1 was significantly improved by the inclusion of PGE_1 with esterified cyclodextrins. It was also disclosed that it could apply to the production of pharmaceuticals of injection-type, aerosol-type, repository-type and oral-type preparations, but there was no disclosure whatsoever on ointment preparations or their drug compositions, nor were there any suggestions whatsoever of them.

Problem(s) to be solved by the invention

However, despite the fact that it is necessary to consider the stability of drug preparations, in particular when the unstable PGE_1 (showing useful pharmaceutical activity) is used as a drug component in drug preparation, there has been almost no investigation of ointment preparations for transdermal application, and the current situation is that there is no ointment preparation with satisfactory stability, transdermal absorbing properties, and drug efficacy.

Means to solve the problem(s)

Therefore, the present inventors have conducted vigorous investigations and many studies aimed at developing PGE_1-containing ointment preparations that satisfy the various aforementioned aspects. That is, based on the conditions of incorporating PGE_1, and having PGE_1 stability over time, it was aimed at developing formulation compositions for ointment base vehicles having better stability and ointment drug formulations having good human transdermal absorption, and furthermore, the most optimum drug that can be applied as an ointment drug for treating subjects having target diseases. As a result, it was discovered that by incorporating PGE_1-ECD into certain ointment base vehicles, the decomposition of PGE_1 was significantly suppressed and also an ointment drug preparation having desirable performance against all the aforementioned drawbacks was obtained, achieving the present invention.

That is, the present invention is one to provide target PGE_1-containing ointment compositions by incorporating PGE_1-ECD in base vehicles formed from saturated fatty alcohols, glycols, and/or absorption accelerators.

To describe the present invention in more detail, the saturated fatty alcohols of the present invention are saturated fatty alcohols having 16-24 carbon atoms or a mixture of them, and are preferably saturated monohydric primary alcohols. Among them, the particularly preferred ones are cetyl alcohol, stearyl alcohol and behenyl alcohol. Additionally, the saturated fatty alcohols are incorporated at 15-45 wt% based on the total weight, and preferably at 20-30 wt%. The glycols are propylene glycol or butylene glycol (preferably 1,3-butylene glycol), and one, or a mixture of two or more, of these are utilized at 50-85 wt% based on the total weight, and preferably at 60-75 wt%. Also, in addition to the aforementioned base vehicle, it is desirable to incorporate absorption accelerators for the purpose of further promoting the absorption efficiency of transdermal absorption. As absorption accelerators, 1-dodecylazacycloheptan-2-one, 1-(2-(decylthio)ethyl)azacycloheptan-2-one, dimethyl sulfoxide, fatty alcohol such as lauryl alcohol or oleyl alcohol, crotamiton, fatty acids such as lauric acid or oleic acid, or terpenes such as l-menthol. Among them, 1-(2-(decylthio)ethyl)azacycloheptan-2-one is the most preferred. The amount of application of the absorption accelerators is 0.01-8 wt% based on the total amount, and it is preferable that 0.1-5 wt% is incorporated.

Also, the effective component PGE_1-ECD is prepared by inclusion of PGE_1 using the esterified cyclodextrins shown below. For examples, there are dimethyl-(α, β or γ)cyclodextrins, hydroxypropyl-(α, β or γ)cyclodextrins, diethyl-(α, β or γ)cyclodextrins, triethyl-(α, β or γ)cyclodextrins and carboxymethylethyl-(α, β or γ)cyclodextrins. Among them, the β-type cyclodextrins are the most preferred for formulating the drug preparations. Also, among the β types, carboxymethylethyl-β-cyclodextrin is the most suitable.

The amount of esterified cyclodextrin for PGE_1 inclusion is 1-300-fold, and preferably, 3-30-fold the amount of PGE_1 utilized, and using that to include 0.0001-1 wt%, but preferably 0.001-1 wt% PGE_1, a better stability can be maintained for the PGE_1. The amount of PGE_1-ECD so obtained is 0.001-10 wt%, and preferably 0.05-5 wt%, in the formulation.

As shown above, an ointment drug preparation suitable for transdermal application and satisfying all the requirements for PGE_1 stability, transdermal absorption, as well as drug efficacy, can be obtained by formulating the aforementioned individual vehicle and the active component and, particularly, by preparing it with the specified formulating compositions. Additionally, other additives may be added to the ointment drug preparation of the present invention according to needs. For examples, in order to improve the stability of PGE_1, organic acids (citric acid, succinic acid, tartaric acid, lactic acid, etc) and supplementary solvents (for examples, polyethylene glycols having molecular weights of 100-800, glycerol, diethylene glycol monoethyl ether, propylene glycol monomethyl ether, dipropylene glycol monoethyl ether, 2,2-dimethyl-1,3-dioxolane-4-methanol, etc.) at under 25 wt%, plasticizers (for examples, polyethylene glycols having molecular weights of 800-20,000, 1,2,6-hexanetriol, sorbitol, etc) at under 15 wt%, coupling agents (for examples, saturated fatty acids having carbon numbers of 16-24 such as stearic acid, palmitic acid and behenic acid, fatty acid amides such as oleamide, palmitamide, stearamide and behenamide, fatty acid esters having carbon number of 16-24 such as sorbitan monostearate and polyethylene glycol monstearate, and other corresponding fatty acid esters of oleic acid and palmitic acid) at under 15 wt% may be incorporated. Also, the amount of formulation of the aforementioned supplementary solvents and plasticizers is preferably 20 wt% or more for the drug preparation.

Moreover, it is preferable that, in addition to the aforementioned vehicles, antioxidants (for examples, ethylene diamine tetraacetic acid, ether chelating agents, propyl gallate, butylated oxyanisole [sic; butylated hydroxyanisole], etc), surfactants, etc. are incorporated to further improve the stability of drug preparation.

Next, in the production of the PGE_1-ECD-containing ointment drug preparation of the present invention, saturated fatty alcohols (15-45 wt%), glycols (50-85 wt%), and according to needs, absorption accelerators (0.01-8 wt%), or other additives are formulated and heated to dissolve at 80-95°C and mixed in the presence or absence of nitrogen gas. The mixture is cooled while mixing at room temperature. This is followed by incorporating the inclusion product (PGE_1-ECD), obtained by dissolving the active component, PGE_1 (0.0001-1 wt%) and the esterified (α, β or γ)-cyclodextrin (0.001-10 wt%) in an organic solvent (for examples, ethanol, methylene chloride, ethyl acetate, etc) and then distilling off the organic solvent, into the vehicle substances in the presence or absence of nitrogen gas, and after agitating and mixing, the target ointment drug preparation of the present invention can be obtained.

Application examples are carried out below to further describe the present invention more specifically.

Application Example 1

Stearyl alcohol 0.95 g, 0.8 g cetyl alcohol, and 0.9 g behenyl alcohol as the saturated fatty alcohols, 7.024 g propylene glycol as the glycol, and 0.3 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator, are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1-carboxymethylethyl-β-cyclodextrin inclusion product, obtained by dissolving 1 mg PGE_1 and 25 mg carboxymethylethyl-β-cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

Application Example 2

Stearyl alcohol 0.95 g, 0.8 g cetyl alcohol and 0.9 g behenyl alcohol as the saturated fatty alcohols, 0.689 g propylene glycol and 6.335 g 1,3-butylene glycol as the glycols, and 0.3 g lauryl alcohol as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1-carboxymethylethyl-β-cyclodextrin inclusion product, obtained by dissolving 1 mg PGE_1 and 25 mg carboxymethylethyl-β-cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

Application Example 3

Stearyl alcohol 0.8 g, 0.6 g cetyl alcohol and 0.6 g behenyl alcohol as the saturated fatty alcohols, 2.145 g propylene glycol and 5.005 g 1,3-butylene glycol as the glycols, and 0.8 g 1-dodecylazacycloheptan-2-one as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1-carboxymethylethyl-β-cyclodextrin inclusion product, obtained by dissolving 1 mg PGE_1 and 49 mg carboxymethylethyl-β-cyclodextrin in ethyl acetate, and then distilling off the ethyl acetate, is added. The target ointment drug preparation is obtained with agitation and mixing.

Application Example 4

Stearyl alcohol 1.0 g and 0.5 g cetyl alcohol as the saturated fatty alcohols, 1.398 g propylene glycol and 5.592 g 1,3-butylene glycol as the glycols, 0.5 g PEG-6000 and 0.3 g

1,2,6-hexanetriol as the plasticizers, 0.2 g sorbitan monostearate as the coupling agent , and 0.01 g oleic acid as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1-dimethyl-β-cyclodextrin inclusion product, obtained by dissolving 0.1 g PGE_1 and 0.4 g dimethyl-β-cyclodextrin in methylene chloride, and then distilling off the methylene chloride, is added. The target ointment drug preparation is obtained with agitation and mixing.

Application Example 5

Stearyl alcohol 2.5 g, 1.0 g cetyl alcohol and 1.0 g behenyl alcohol as the saturated fatty alcohols, 3.735 g propylene glycol and 1.265 g 1,3-butylene glycol as the glycols, 0.1 g 1,2,6-hexanetriol as the plasticizer, 0.10 g polyethylene glycol monostearate as the coupling agent , and 0.27 g l-menthol as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this basic vehicle, a PGE_1-triethyl-β-cyclodextrin inclusion product, obtained by dissolving 100 μg PGE_1 and 0.03 g triethyl-β-cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

Application Example 6

Stearyl alcohol 1.50 g as the saturated fatty alcohol, 0.84 g propylene glycol and 7.56 g 1,3-butylene glycol as the glycols, and 0.05 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1-carboxymethylethyl-β-cyclodextrin inclusion product, obtained by dissolving 10 mg PGE_1 and 40 mg diethyl-β-cyclodextrin in ethyl acetate, and then distilling off the ethyl acetate, is added. The target ointment drug preparation is obtained with agitation and mixing.

Application Example 7

Stearyl alcohol 1.0 g and 0.8 g cetyl alcohol as the saturated fatty alcohols, 6.4 g 1,3-butylene glycol as the glycols, 0.2 g sorbitan monostearate as the coupling agent, and 0.5 g PEG-6000 as the plasticizer are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1-hydroxypropyl-β-cyclodextrin inclusion product, obtained by dissolving

100 mg PGE_1 and 1 g hydroxypropyl-β-cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

Application Example 8

Stearyl alcohol 0.95 g, 0.8 g cetyl alcohol and 0.9 g behenyl alcohol as the saturated fatty alcohols, 6.924 g propylene glycol as the glycol, 0.3 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator, and 0.1 g lactic acid as the stabilizing agent are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1-carboxymethylethyl-β-cyclodextrin inclusion product, obtained by dissolving 1 mg PGE_1 and 25 mg carboxymethylethyl-β-cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

Application Example 9

Stearyl alcohol 1.0 g and 0.5 g cetyl alcohol as the saturated fatty alcohols, 1.398 g propylene glycol and 5.592 g 1,3-butylene glycol as the glycols, 0.5 g PEG-6000 and 0.3 g 1,2,6-hexanetriol as the plasticizers, 0.1 g sorbitan monostearate as the coupling agent, 0.01 g oleic acid as the absorption accelerator, and 0.1 g lactic acid as the stabilizing agent are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1-dimethyl-β-cyclodextrin inclusion product, obtained by dissolving 0.1 g PGE_1 and 0.4 g dimethyl-β-cyclodextrin in methylene chloride, and then distilling off the methylene chloride, is added. The target ointment drug preparation is obtained with agitation and mixing.

Application Example 10

Stearyl alcohol 2.5 g, 0.99 g cetyl alcohol and 1.0 g behenyl alcohol as the saturated fatty alcohols, 3.735 g propylene glycol and 1.265 g 1,3-butylene glycol as the glycols, 0.10 g 1,2,6-hexanetriol as the plasticizer, 0.10 g polyethylene glycol monostearate as the coupling agent, 0.27 g l-menthol as the absorption accelerator, and 0.01 g lactic acid as the stabilizing agent are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1-triethyl-β-cyclodextrin inclusion product, obtained by dissolving 100μg PGE_1 and 0.03 g triethyl-β-cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

Application Example 11

Stearyl alcohol 1.5 g as the saturated fatty alcohol, 0.83 g propylene glycol and 7.47 g 1,3-butylene glycol as the glycols, 0.05 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator and, 0.1 g lactic acid as the stabilizing agent are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1-diethylethyl-β-cyclodextrin inclusion product, obtained by dissolving 10 mg PGE_1 and 40 mg diethyl-β-cyclodextrin in ethyl acetate, and then distilling off the ethyl acetate, is added. The target ointment drug preparation is obtained with agitation and mixing.

Application Example 12

Stearyl alcohol 1.0 g and 0.8 g cetyl alcohol as the saturated fatty alcohols, 6.0 g 1,3-butylene glycol as the glycol, 0.5 g PEG-6000 as the plasticizer, 0.2 g sorbitan monostearate as the coupling agent, and 0.5 g lactic acid as the stabilizing agent are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1-hydroxypropyl-β-cyclodextrin inclusion product, obtained by dissolving 100 mg PGE_1 and 0.9 g hydroxypropyl-β-cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

Comparative Example 1

Stearyl alcohol 0.95 g, 0.8 g cetyl alcohol and 0.9 g behenyl alcohol as the saturated fatty alcohols, 0.704 g propylene glycol and 6.345 g 1,3-butylene glycol as the glycols, and 0.3 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, 1 mg PGE_1 is added. The target ointment drug preparation is obtained with agitation and mixing.

Comparative Example 2

Stearyl alcohol 0.95 g, 0.8 g cetyl alcohol and 0.9 g behenyl alcohol as the saturated fatty alcohols, 0.704 g propylene glycol and 6.320 g 1,3-butylene glycol as the glycols, and 0.3 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE_1- β-cyclodextrin inclusion product, obtained by dissolving 1 mg PGE_1 and 25 mg β-cyclodextrin in ethanol, and then

distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

Comparative Example 3

White vaseline 8.299 g, 0.8 g bleached beeswax, 0.3 g stearyl alcohol, 0.3 g cholesterol, and 0.3 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator are added together and heated to dissolve in an water bath with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, 1 mg PGE_1 is added. The target ointment drug preparation is obtained with agitation and mixing.

Experimental Example 1 Stability Test

In order to investigate the stability of PGE_1 in the ointment drug preparations of the present invention, 2 g each of the ointment of Application Examples 1-12 and those of Comparative Examples 1-3 were filled in aluminum tubes coated on the inner side with phenol resin, and after storing for 40 days at 40°C in a constant-temperature oven, the residual amounts of prostaglandin were quantified by liquid chromatography. A column filled with octadecylsilylated silica was used for the liquid chromatography, the moving phase was a mixed solution of 0.01M KH_2PO_4-acetonitrile, and detection was conducted at 201 nm. The results are shown in Table 1.

Table 1

① 試　　料	PGE$_1$ 残存率 (%) ②
実施例 1 の軟膏製剤	89.6
実施例 2 の軟膏製剤	89.4
実施例 3 の軟膏製剤	89.2
実施例 4 の軟膏製剤	75.8
実施例 5 の軟膏製剤	78.6
実施例 6 の軟膏製剤	73.1
実施例 7 の軟膏製剤	72.1
実施例 8 の軟膏製剤	88.6
実施例 9 の軟膏製剤	85.9
実施例10の軟膏製剤	86.7
実施例11の軟膏製剤	82.4
実施例12の軟膏製剤	88.7
比較例 1 の軟膏製剤	44.7
比較例 2 の軟膏製剤	39.3
比較例 3 の軟膏製剤	21.6

③ (spans the Application Example rows)

④ (spans the Comparative Example rows)

Key: 1 Sample
2 Residual rate
3 Ointment drug preparation of Application Example__
4 Ointment drug preparation of Comparative Example__

By comparing the results of the ointment drug preparations of the present invention to those of Comparative Examples 1, 2, and 3, it was found that decomposition of PGE_1 was significantly suppressed by carrying out the inclusion of PGE_1 in esterified cyclodextrins.

Experimental Example 2 Skin blood flow rate test

In order to confirm the localized efficacy of the ointment drug preparations of the present invention, determination of skin blood flow rate was conducted.

The compositions obtained in Application Example 1 and Comparative Examples 1 and 2 were applied openly, at 10 mg each, on a 1 x 1 cm area of the back skin of hairless mice anesthesized with urethane. The blood flow rate was determined before application and at 5 min intervals until 2 h after application, using a doppler laser blood flow meter. The differences (ml/min/100 g) before and after application were determined and used as the results, which are shown in Figure 1.

From the test results, it was found that the ointment drug preparations of the present invention showed significant increases of skin blood flow, compared to the case of Comparative Example 1, where PGE_1 was not included in esterified cyclodextrin, and to Comparative Example 2, where it was included in β-cyclodextrin; additionally, it was found that the activity was maintained until 2 h after application, showing that the ointment drug preparation of the present invention were sufficiently absorbed transdermally and exerting sufficient drug efficacy.

Function and effect of the invention

The ointment drug preparations of the present invention are the first-ever achieved ointment compositions using the combination of PGE_1-ECD and specific ointment vehicles. Additionally, as it is clear from the result of the aforementioned stability test, the decomposition of PGE_1 is significantly suppressed because the PGE_1 included in esterified cyclodextrins is formulated into the ointment base vehicles, resulting in a very desirable drug preparation. Furthermore, the drug preparations are extremely stable so that they can be stored for a long period of time, and therefore, they are desirable for quality control purposes and are suitable for product commercialization. Additionally, the skin blood flow test rate showed a significant increase of skin blood flow and it was also found that the effect could be maintained for a few hours. This sufficiently underscores the fact that the ointment drug preparations of the present invention are smoothly absorbed transdermally, which results in the expression of the drug efficacy. Thus it is desirable for formulating drug preparations.

Accordingly, the ointment drug preparations of the present invention are extremely superior in terms of stability of PGE_1, expression of pharmacological activity and transdermal absorption properties. As ointment drug preparations for the purposes of local application, they can be expected to be utilized in the treatment of Raynaud's disease, decubitus, skin ulcer, psoriasis, arteriosclerosis, etc., as well as being applied as a drug for hair growth.

Particularly, that the problem of stabilizing PGE_1 is solved, which is the necessary condition for ointment drug preparations, is a matter of utmost importance in the drug preparation and is extremely useful to the pharmaceutical industry.

Brief description of the figure

Figure 1 shows the experimental results of skin blood flow when the drug preparations of the present invention are applied locally. The vertical axis shows the difference of blood flow rate before and after application of the compositions while the horizontal axis shows the lapsed time after application of the compositions.

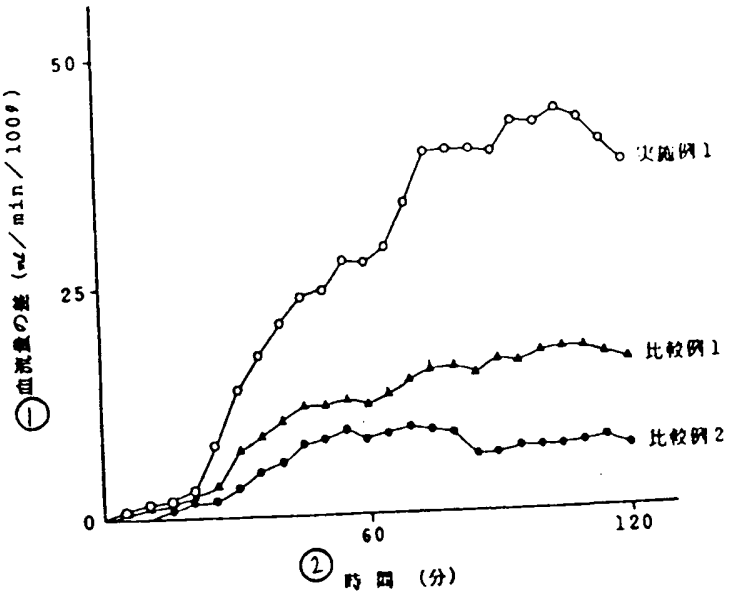


Figure 1

Key: 1 Difference in blood flow rate
2 Time